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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 4

Application Number: 09/027,439
Filing Date: February 20, 1998
Appellant(s): PORTUGAL ET AL.

Richard J. Traverso
For Appellant

EXAMINER'S ANSWER

This is in response to the substitute appeal brief filed February 2, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Issue 1) The examiner has withdrawn the objection to the specification with regard to Table 2 having entries that are not identified by a SEQ ID NO. Upon further review, it was determined that because each different entry has a SEQ ID NO, any entry with a duplicate sequence does not have to set forth the SEQ ID NO for that entry because the SEQ ID NO can be determined from the entries already in the Table. Issue 2) The examiner has withdrawn the objection to claim 58 under 37 CFR 1.75(c). Therefore, the first and second issues listed in the issues section of appellant's brief are moot. It is noted that these Issues 1 and 2, are directed to issues relating to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201. With regard to Issue 6, the brief lists the accession

numbers cited by the examiner as being from Chembank, however these are Genbank accession numbers.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,541,308 Hogan et al 7-1996

Genbank Accession Number X96964, February 4, 1996

Genbank Accession Number X80726, March 29, 1996

Cilia et al; Mol. Biol. Evol. Vol. 13, pp 451-461; published 2/20/1996

Genbank Accession Number A14565, September 29, 1994

Dyson, N.J. from Essential Molecular Biology Vol. II: A Practical Approach, Chapter 5, pages 111-156; Brown, T.A. ed. Oxford University Press, 1992

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

1. Claims 55-58 are rejected are under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 55-58, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Response to Arguments

Applicant's arguments have been fully considered but are not found persuasive. The response asserts that claims 55-58 are drawn to compositions of matter which are useful as investigative tools and clearly fall within the subject matter defined by the statute and that because no evidence has been presented that these sequences exist in nature by the lack of relevant prior art under 35 USC 102 and 103, the probes of varying length are inherently distinguished from any subject alleged to be found in nature. This argument was not found persuasive because the fact that a substance, such as a cell or a nucleic acid, can be used for an investigative tool does not exclude it from also occurring in nature. A cell occurs in nature, for example a bacterial cell such as *E. coli* or a species of *Shigella*, but the cell can also be used as an investigative tool, for example to express proteins from the same or other organisms. Nucleic acids can occur in nature, for example an rRNA sequence would exist in a cell in nature, and could also be used to construct sequences for identification of a particular organism. In the instant case, the claimed nucleic acids are not limited to any particular upper length limitation because of the recitation of "greater than 10 to 40 nucleotides in length" (claims 55 and 56) and

"comprises 15-25 bases in length" (claims 57 and 58). Further, the specification does not limit the recitation of "probe" to any particular upper length limitation and specifically defines the term as "a synthetic *or biologically produced* nucleic acid" (see p. 17, lines 10-11). Therefore, although the claimed nucleic acids include molecules that were constructed with specific lengths for use as a diagnostic reagent, they also encompass full length rRNA molecules (the claims in question recite 'RNA equivalent thereof") that do exist in a cell and are biologically produced, as well as a full chromosomes which also exist in a cell and are biologically produced. As the specification teaches that the sequences SEQ ID NO 3-6 are the 16S rRNA sequences from strains of 4 different species of *Shigella*, it is unclear why more evidence is required to determine that the sequences encompassed by the claims also encompass sequences that exist in nature.

Claim Rejections - 35 USC § 112

2. Claims 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 55 and 56 recite the limitation "greater than 10 to 40 bases in length". Such recitation is indefinite because it is unclear if a nucleic acid of 15 (for example, recited in claims 57 and 58) bases in length would meet the limitation of the claims as such is less than 40 bases. Consequently, the metes and bounds of the claims are unclear.

The recitation of "said molecule" in claims 55 and 56 lacks sufficient antecedent basis. The claims are drawn to a "probe" and do not recite the word molecule, therefore it is unclear if

the recitation of "complementary to said molecule" refers to a nucleic acid that is complementary to the probe, or just to the fragment that the probe comprises.

Response to Arguments

Applicant's arguments have been fully considered but are not found persuasive. The response asserts that the language "greater than 10 to 40 bases in length" can only be interpreted to define a range having a lower limit of greater than 10 bases in length and an upper limit of 40 bases in length. This argument was not found persuasive because the claim can be interpreted a number of different ways. The claim can be interpreted to encompass greater than "10 to 40" bases. In such a case, 50 nucleic acid would be greater than "10 to 40" but 15 would not be greater than "10 to 40" because 15 nucleic acid would be *within* the range of 10-40, not greater than the range. The claim could also be interpreted to encompass any number of lower length limitations, ie: greater than 10, greater than 11, greater than 12... greater than 39, greater than 40 bases in length. In such case, the claim only recites different lower length limitations and no upper length limitations. The claim could also be interpreted to encompass a nucleic acid greater than 10, and up to 40 bases in length, as the response asserts. However, the claim does not recite "up to 40". Additionally, even if the recitation of 'up to 40' were included in the claim, the upper length would still be in question because of the use of the term "comprising", which is considered 'open' terminology, that is it encompasses sequences on either side of the defined sequence (a nucleic acid 'comprising' SEQ ID NO: 1, encompass sequences that contain SEQ ID NO: 1 but also can contain an unlimited number and identity of bases on either side of SEQ ID NO: 1). The response asserts that claim 56 is more definite because of the use of "consisting of". This argument was not found persuasive because while the term "consisting of" is considered

'closed' terminology, that is it does not encompass sequences on either side of the defined sequence (a nucleic acid 'consisting' of SEQ ID NO: 1 only encompasses the sequence of SEQ ID NO: 1), the use of the word 'greater' seems to contravert the 'closed' language of 'consisting of'. In other words, a probe 'consisting of greater than 10 to 40 bases in length' can encompass greater than 40 bases in length. As such, the analysis used above for claim 55 applies, and the metes and bounds of the length of the claimed nucleic acid is unclear.

The response does not provide any arguments with regard to the recitation of "said molecule" lacking antecedent basis.

Claim Rejections - 35 USC § 102

3. Claims 47, 48, 53, and 55-58 are rejected under 35 U.S.C. 102(a) and 102 (e) as being anticipated by Hogan (US Patent 5,541,308: 102(a) date -July 30, 1996; 102(e) date – 12/9/1988).

Instantly claimed SEQ ID NOS 3-6 are rRNA sequences of *Shigella flexneri, sonnei, dysenteriae, and boydii*, respectively.

Hogan teaches a probe which detects *E. coli* (see col. 52, line 17) (hereinafter termed "Sequence A") which is completely complementary to positions 991-1120 of SEQ ID NO 3, and positions 989-1018 of SEQ ID NO 6. Sequence A of Hogan also has complementary sequences to both SEQ ID NO 4, over positions 990-1019, and SEQ ID NO 5 over positions 990-1019. Hogan teaches another sequence (see col. 52, lines 24-25) (hereinafter termed "Sequence B") which is completely complementary to positions 955-993 of SEQ ID NO 3, positions 954-992 of SEQ ID NO 5, and positions 953-991 of SEQ ID NO 6. With regard to positions 955-992 of

SEQ ID NO 4, position 36 of the complement of Sequence B taught by Hogan contains a mismatch with position 958 of SEQ ID NO 4 and position 22 of the complement of Sequence B taught by Hogan contains an insertion between positions 971 and 972 of SEQ ID NO 4.

With regard to amended claims 47, 48, and newly added claims 53, and 55-58, Sequences A and B taught by Hogan are "capable of base pairing to SEQ ID NOS 3-6" according to the standard Watson Crick complementarity rules" (no conditions are specified in the claim). This recitation is not considered to limit the claimed nucleic acid to completely complementary sequences or full complements of SEQ ID NOS 3-6. With regard to claims 55 and 56, Sequence A taught by Hogan is 30 bases, and Sequence B taught by Hogan is 39 bases, and therefore these sequences are "greater than 10 bases" in length. With regard to claims 57 and 58, the sequences taught by Hogan "comprises" 15-25 bases.

With regard to amended claims 47 and 48, sequence A taught by Hogan is capable of hybridizing to SEQ ID NOS 3 and 6, and sequence B taught by Hogan is capable of hybridizing to SEQ ID NOS 3, 5, and 6 under the conditions specified as they are completely complementary to sequences within SEQ ID NOS 3, 5, and 6. Further, with regard to the recitation of "targets" in claims 55 and 56, this term is broadly interpreted to encompass probes which will hybridize to or detect species of *Shigella*, which are considered inherent properties of the sequences taught by Hogan as Hogan teaches that Sequence A reacts with *Shigella* species (see col. 52, lines 47-49, and table 54), and the sequences are completely complementary to sequences within SEQ ID NOS 3, 5, and 6 and would hybridize to and detect SEQ ID NOS 3, 5, and 6.

Response to Arguments

Applicant's arguments have been fully considered but are not found persuasive. The response asserts that providing a complementary sequence to only a portion of SEQ ID NO: 3, 4, 5, and 6 does not anticipate the molecules and probes of claims 47, 48, 53, or 55-58. This argument was thoroughly reviewed but was not found persuasive because the specification does not define the term 'complementary to SEQ ID NO: X' to be limited to a sequence that is completely complementary over the full length of SEQ ID NO: X. The specification defines the term "complementary" to mean a sequence that is capable of base pairing according to the standard Watson Crick complementary rules (see page 14, line 10). Such refers to the hybridization of two sequences. A nucleic acid that is 30 nucleotides long and contains one or a few mismatches (termed for the sake of argument, Sequence X) with but would otherwise be completely complementary over it's full length with another sequence (Sequence Y, which is 1000 nucleotides long) would be 'capable of base pairing according to the standard Watson Crick complementary rules' to Sequence Y because the length of the Sequences X and Y and the fact that all but one base or a few bases are mismatched between the two would override the effect of the mismatch(s) under many hybridization conditions, and there would be normal base pairing between the sequences that matched with their complements. In cases where the claims recite "capable of base pairing under the normal Watson Crick complementarity rules", no hybridization or wash conditions are specified. Therefore, under certain conditions, the nucleic acids sequences would be 'capable of base pairing according to the standard Watson Crick complementarity rules' and the sequences taught by Hogan meet the claim limitations (this applies to claims 47, 48, 53, and 55-58 which all recite this limitation). Additionally, even if

'capable of base pairing according to the standard Watson Crick complementarity rules' were defined by the specification to mean sequences that contain no mismatches, the specification still does not define the term complementary to be limited to sequences which are complementary to each other over their entire length. Therefore, even under such considerations, the sequences of Hogan still meet the claim requirements because they are themselves completely complementary to regions within SEQ ID NOS 3, 5, and 6. Even under highly stringent hybridization and wash conditions, the sequences of Hogan are capable of base pairing under the standard Watson Crick complementarity rules to SEQ ID NOS 3, 5, and 6.

Also, specifically with regard to claims 55-58, it is further noted that claims are not limited to the complete sequences of SEQ ID NOS 3-6 but encompass fragments and sequences which are complementary to either the fragments or the probe comprising the fragments. Applicant's argument does not apply to these claims under such embodiments and it is unclear how the sequences of Hogan would not meet the claim limitations because the sequences of Hogan are completely complementary over the full length of fragments of SEQ ID NOS 3, 5, and 6. Further, the sequences of Hogan 'comprise 15-25 bases in length'.

4. Claims 47, 48, 53, and 55-58 are rejected under 35 U.S.C. 102(a) as being anticipated by (in the alternative) Genbank accession numbers X96964 (4/4/96), or X80726 (3/29/1996, disclosed in Cilia et al 2/20/1996).

Instantly claimed SEQ ID NOS 4 is an rRNA gene sequence of *Shigella sonnei.*

Accession numbers X96964, and X80726 teach rRNA gene sequences of *Shigella sonnei.* (It is noted that sequence alignments with the claimed sequences are provided):

With regard to amended claims 47, 48, and newly added claims 53, and 55-56, the complements of the accession numbers are "capable of base pairing to SEQ ID NOS 4 according to the standard Watson Crick complementarity rules" (no conditions are specified in the claim). This recitation is not considered to limit the claimed nucleic acid to completely complementary sequences or the full complement of SEQ ID NOS 4. Additionally, with regard to claim 55, accession number X96964 is 1488 base pairs and accession number X80679 is 1467 base pairs. Such sequences comprise a fragment "greater than 10 bases to 40 bases of SEQ ID NO 4". With regard to claims 57 and 58, the accession numbers "comprises" 15-25 base pairs. Further, as these sequences are rRNA sequence of *Shigella sonnei*, the complements of such would necessarily "target" *Shigella sonnei*.

Also, with regard to amended claims 47 and 48, the complements of the accession numbers are considered "substantially complementary" to the claimed SEQ ID NO and would be capable of hybridizing to the SEQ ID NO under the recited conditions. The recitation of "substantially complementary... capable of hybridizing" to the nucleic acid molecule is not sufficient to distinguish the claimed nucleic acids from the complement of the accession numbers. Firstly, the claim's amended recitation of "substantially complementary" necessarily stipulates that such sequences are not necessarily fully complementary or complete complements of the recited SEQ ID NOS. Secondly, the specification teaches at page 17, that such conditions could tolerate mismatches, and further at page 33, "the effect of a one base mismatch is decreased with a longer probe". SEQ ID NO 4 and accession number X96964 contain 5 mismatches. The complement of the accession number would hybridize to SEQ ID NO 4 because the effect of the 5 mismatches would be diminished due to the length of the accession

number (1488 base pairs). SEQ ID NO 4 and accession number X80726 contain 10 mismatches. The complement of the accession number would hybridize to SEQ ID NO 4 because the effect of the 10 mismatches would be diminished due to the length of the accession number (1467 base pairs).

Note: the accession numbers teach the 16S rRNA "gene" (see "Definition") which is considered double stranded. Although the accession numbers do not specifically recite the complement, such is considered an inherent teaching of a "gene".

Response to Arguments

Applicant's arguments have been fully considered but are not found persuasive. The response asserts that because the accession numbers do not specifically recite the complement, they cannot anticipate any of the complementary sequences claimed herein. This argument was not found persuasive because Genbank does not recite the complement of a gene sequence, even when a gene sequence (DNA sequence occupying a discrete locus on a chromosome, which is double stranded and contains a sense strand and an antisense strand) is provided as in the instant case. It is further noted that Genbank distinguishes when a gene vs an RNA (a single stranded molecule) sequence is provided (see rejection under 35 USC 103 (a), provided below). The fact that Genbank does not actually recite the complement (the antisense strand) does not indicate that it does not exist or was not provided. Further, where the claims recite fragments "greater than 10 to 40 nucleotides in length", this argument does not apply. The sequences of the accession numbers are "greater than 10 to 40 bases in length" of a nucleotide sequence of SEQ ID NO: 4 and "comprise 15 to 25 bases in length".

Claim Rejections - 35 USC § 103

5. Claims 47, 48, 53, and 55-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Accession number A14565 (September 29, 1994) in view of Dyson, N.J. (Essential Molecular Biology Vol. II: A Practical Approach, chapter 5, pages 111-156, Brown, T.A. ed. Oxford University Press, Oxford, 1992).

Accession number A14565 teaches a sequence of 16S rRNA from E. Coli.

With regard to amended claims 47, 48, and newly added claims 53, and 55-56, the complement of the accession number is "capable of base pairing to SEQ ID NO 3 according to the standard Watson Crick complementarity rules" (no conditions are specified in the claim). This recitation is not considered to limit the claimed nucleic acid to completely complementary sequences or the full complement of SEQ ID NOS 3. Additionally, with regard to claim 55, the accession number is 1541 base pairs. Such sequence comprises a fragment "greater than 10 bases to 40 bases of SEQ ID NO 3". With regard to claims 57 and 58, the accession number "comprises" 15-25 base pairs. With regard to the recitation of "targets *Shigella flexneri*", (claims 55 and 56) such recitation is broadly interpreted to encompass sequences that could hybridize to *Shigella flexneri* (see paragraph below).

Also, with respect to amended claims 47 and 48, the complement of the accession number is considered "substantially complementary" to the claimed SEQ ID NOS and would be capable of hybridizing to the SEQ ID NOS under the recited conditions. The recitation of "substantially complementary... capable of hybridizing" to the nucleic acid molecule is not sufficient to distinguish the claimed nucleic acids from the complement of the accession numbers. Firstly, the claim's amended recitation of "substantially complementary" necessarily

stipulates that such sequences are not necessarily fully complementary or complete complements of the recited SEQ ID NOS. Secondly, the specification teaches at page 17, that such conditions could tolerate mismatches, and further at page 33, "the effect of a one base mismatch is decreased with a longer probe". The sequence of accession number A14565 contains only 5 mismatches and a gap of 1 nucleotide with respect to the entirety of SEQ ID NO 3 (sequence alignment provided). The complement of the accession number would hybridize to SEQ ID NO 3 because the effect of the 4 mismatches would be diminished due to the length of the accession number (1541 base pairs).

Although accession number A14565 does not teach the full complement of the sequence, it would have been prima facie obvious to one of ordinary skill in the art to construct the full complement of accession number A14565 to obtain a probe that would hybridize to accession number A14565 for the purposes of detecting accession number A14565. Such methods were readily used in the art at the time of the invention, as exemplified by Dyson, which teaches constructing probes for the purposes of hybridization detection assays.

Response to Arguments

Applicant's arguments have been fully considered but are not found persuasive. The response asserts that the combined teachings do not show or suggest SEQ ID NOS 3, 4, 5, or 6 and therefore do not show or suggest their complements. This argument was not found persuasive because the rejection did not set forth that the complement of the accession number was either the sequence of any of SEQ ID NOS 3-6, or their full complements. The response argues that because 'complementary' and 'substantially complementary' are contained within the same claim in claims 47 and 48, that such recitation was redundant if both defined sequences that

were not complete. This argument was not found persuasive because it is permissible for applicants to claim embodiments in a single claim that could overlap in scope. The recitation of hybridization and wash conditions with the recitation of 'substantially complementary' would in some cases encompass sequences that would not overlap in scope with sequences that would be 'complementary' but capable of base pairing according to the standard Watson Crick complementarity rules where no conditions are specified. The response asserts that there is no evidence that it would be obvious to prepare a sequence completely complementary or substantially complementary to SEQ ID NOS 3-6, however the rejection did not assert that it would be obvious to construct the complement of the accession number to detect or hybridize to SEQ ID NOS 3-6, but that it would be obvious to do so to detect or hybridize to the sense strand of the accession number. The fact that such a sequence would also hybridize to SEQ ID NOS 3-6 does not indicate that the examiner used hindsight reasoning. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the examiner did not use applicant's invention to provide motivation for construction of the complement of the accession number because at the time of filing of the instant invention, it was already well known that the complement of a sequence could be used in

a hybridization assay to detect the sequence. Such methods were also readily used as exemplified by the teachings of Dyson.

(11) Response to Argument

The response to each of appellant's arguments is set forth above, following each individual rejection.

For the reasons set forth above, it is believed that the rejections should be sustained.

Respectfully submitted,

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